Plasma creatinine medians from patients partitioned by gender and age used as a tool for assessment of analytical stability at different concentrations

Hansen, Steen Ingemann; Petersen, Per Hyltoft; Lund, Flemming; Fraser, Callum G.

Published in:
Clinical Chemistry and Laboratory Medicine (CCLM)

DOI:
10.1515/cclm-2019-0334

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Steen Ingemann Hansen*, Per Hyltoft Petersen, Flemming Lund and Callum G. Fraser

Plasma creatinine medians from patients partitioned by gender and age used as a tool for assessment of analytical stability at different concentrations

https://doi.org/10.1515/cclm-2019-0334
Received March 26, 2019; accepted July 12, 2019

Abstract

Background: Monthly medians of patient results are useful in assessment of analytical quality in medical laboratories. Separate medians by gender makes it possible to generate two independent estimates of contemporaneous errors. However, for plasma creatinine, reference intervals (RIs) are different by gender and also higher over 70 years of age.
Methods: Daily, weekly and monthly patient medians were calculated from the raw data of plasma creatinine concentrations for males between 18 and 70 years, males >70 years, females between 18 and 70 years and females >70 years.
Results: The medians of the four groups were all closely associated, with similar patterns. The mean of percentage bias from each group defined the best estimate of bias. The maximum half-range (%) of the bias evaluations provided an estimate of the uncertainty comparable to the analytical performance specifications: thus, bias estimates could be classified as optimum, desirable or minimum quality.
Conclusions: Medians by gender and age are useful in assessment of analytical stability for plasma creatinine concentration ranging from 60 to 90 μmol/L. The daily medians are valuable in rapid detection of large systematic errors, the weekly medians in detecting minor systematic errors and monthly medians in assessment of long-term analytical stability.

***Corresponding author: Steen Ingemann Hansen,** Department of Clinical Biochemistry, Nordsjællands Hospital, University of Copenhagen, Dyrehavevej 29, 3400 Hillerød, Denmark, Phone: +004548294156, Fax: +004548294184, E-mail: Steen.Ingemann.Hansen@Regionh.dk
Per Hyltoft Petersen: Department of Clinical Biochemistry, Nordsjællands Hospital, University of Copenhagen, Hillerød, Denmark; and Norwegian Quality Improvement of Laboratory Examinations (NOKLUS), Haraldsplass Deaconess Hospital, Bergen, Norway
Flemming Lund: Department of Clinical Biochemistry, Nordsjællands Hospital, University of Copenhagen, Hillerød, Denmark
Callum G. Fraser: Centre for Research into Cancer Prevention and Screening, University of Dundee, Dundee, Scotland

Keywords: analytical stability; medians of plasma creatinine; partitioning by gender and age; percentage bias; raw data for plasma creatinine.

Introduction

Plasma concentrations of creatinine are important in the diagnosis of kidney diseases, detection of acute kidney injury and monitoring of patients with renal impairment or failure, and it is usually requested by general practitioners (GP) together with plasma electrolytes and metabolites as a form of case-finding or screening in patients. The analytical quality of plasma creatinine examinations is therefore critical in many clinical settings, so methods to assess the ongoing performance of the examinations are necessary.

A valid method to assess the analytical stability of quantitative examinations in laboratory medicine is the use of monthly patient medians of the results of examinations on samples from patients [1]. In a previous study, we applied the half-range, as a percentage, of monthly medians from all patients as an estimate of the maximum bias [2]. Traditionally, the monthly medians were based on all patient results, but recently we have improved the model for serum sodium by separating the medians by gender [3].

For serum sodium [3] and serum albumin [4], the ratios between the monthly medians by gender were very stable in spite of considerable, but parallel, variation of the medians by separate gender due to the current analytical variation. Consequently, if the mean of the percentage deviations of the two medians from their targets was used as an estimate of the bias (more correctly: change in bias – Δbias), then the half-range (%) of the ratios of medians by gender was an estimate of the maximum deviation of the mean of the bias from the accurate Δbias estimate [4].

In order to obtain objective analytical performance specifications (APS) for the analytical stability, we used the APS for bias, based on biological variation and the requirement to share common reference intervals (RIs), from Fraser et al. [5], with three levels of quality.

For serum sodium [3] and serum albumin [4], the ratios of medians by gender (females/males) both approximate to 1.000, but this gives only assessment of a single concentration range. However, the measur- and plasma creatinine has different RIs for adult males and females, with RIs in the Nordic countries for males: 62.4–100.7 µmol/L, and for females: 50.5–87.5 µmol/L [6]. In contrast, in a later publication from Uppsala, Sweden, unselected 70-year-old males and females showed higher RIs of 59–125 µmol/L and 45–103 µmol/L, respectively [7]. This led to the concept of assessing the stability of plasma creatinine examinations by calculating the patient medians of separate subgroups, partitioned according to gender and also age.

The aim of the current investigation was therefore to examine the usefulness of patient medians of plasma creatinine for daily, weekly and monthly assessment of analytical stability of examinations by use of raw data from four patient groups. The targets were previous medians for four groups: males 18–70 years (M 18–70), males >70 years (M >70), females 18–70 years (F 18–70), and females >70 years (F >70). Fractional bias (ϕbias) and percentage bias of the individual groups, and the four combined, were calculated.

Materials and methods

Analysers and results of examination of samples from patients

The Department of Clinical Biochemistry, Nordsjællands Hospital, University of Copenhagen, generated 205,573 plasma creatinine results for the first 6 months of 2018 from patients >18 years; 55% were requested by a GP. Creatinine concentrations were examined by use of ECREA (enzymatic) on three Siemens Dimension Vista® 1500 instruments (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) with calibrators and reagents from Siemens.

The study included all results from samples from male and female patients who were >18 years of age, with a Danish personal identification number, collected on working days (weekends and holidays were excluded to ensure a homogenous population).

From 1 April 2017, the results of the examinations were retained as the raw data from the analysers to allow the computations and calculations of medians used in the model. Sampling was changed from serum to lithium heparinised plasma for creatinine between 10 and 18 September 2017.

The overall monthly (2018) analytical coefficient of variation (CV_A) was 2.1% (n = 553, mean = 124.2 µmol/L). These data are on a lyophilised human serum pool (HK18) that was produced by Randox Laboratories Ltd (Crumlin, UK) and obtained from the Danish Institute for External Quality Assurance for Laboratories in Health Care, DEKS (DEKS, Rigshospitalet-Glostrup, Glostrup, Denmark).

The routine procedures for serum and plasma creatinine examinations were not changed during the study nor during the subsequent assessment of the model.

Calculations

The calculations were performed as documented for serum sodium [3] and serum albumin [4]. Briefly, the raw results from the examinations on samples from patients were used for calculation of daily, weekly and monthly medians of results for each of four groups according to gender and age: (M 18–70), (M >70), (F 18–70) and (F >70) calculated for each analyser and for the three analysers combined. The medians from 1 April to 31 December 2017 for the four groups on all instruments were used as estimates of the stable medians and therefore applied as target (T) values in the calculations of bias for daily, weekly and monthly medians during the first 6 months of 2018, (100 * {median – T}/T). The medians from 2014 to 31 March 2017 (as integers) were also calculated in order to validate the previous stability. We also calculated the individual bias from the three instruments for the four groups and their mean bias. During the investigation, the instrument Vista 3 showed minor deviating results (illustrated in Figure 3B), and this is considered further in the Discussion.

Validation of bias based on classification of patients by reference intervals (RI)

We used the APS for bias from Fraser et al. [5], with the three levels of quality, optimum, desirable and minimum quality. We used recently published data on biological variation of plasma creatinine from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) (EuBIVAS) [8]. These APS for bias are used for classification in the tables as the following numbers: “1”, optimum for half-range <1.8%, “2”, desirable for half-range <3.6%, “3”, minimum quality for half-range <5.4%, and “4” for larger half-ranges.

Deviations of estimated ϕbias and percentage bias

The four medians are different in concentration, but a reasonable assumption is that the results of the examinations are proportional and also that the errors are proportional with the same fractional bias (ϕbias) or in percentage: bias = 100 * (ϕbias – 1).

Determination of medians of creatinine and dispersions of distributions

The requesting of creatinine is initiated outside the laboratory for a variety of clinical rationale and, in consequence, the data on results can be considered as random. Each median of the creatinine is termed and designated true plasma creatinine (T_G) and the dispersion described by a standard error (SE_G), defined by the selected group and the number of individuals therein. Thus, the T_G is totally independent of the analytical performance for each group

under investigation, but the magnitude of the dispersion of the distribution depends on SE_G.

Target values

Target values are the medians calculated from the raw measurements of serum and plasma creatinine results in 2017 from 1 April. They are denoted measured targets (T_M), and are specific for the local patient sample and the analytical performance in 2017 during the collection period and with the actual number of samples. The assumption is that the analytical performance and ϕbias are the same for the four groups, so $T_M = T_G * \phi bias_{2017}$ where T_M is defined as a target for medians determined in 2018.

Raw results from the examinations on samples from patients

The calculated raw medians (M_C) of the four groups in 2018 are based on two constituents: the T_G (with corresponding SE_G) and the analytical performance attained (depending on instruments, calibrations, reagents and maintenance: the imprecision (ε) is negligible for the medians): $M_C = T_G * \phi bias_{2018}$ and the fractional bias of the target compared to 2017 is $\phi bias_{2018}/\phi bias_{2017}$, which is simply denoted "ϕbias" in the following since the bias of T_M ($\phi bias_{2017}$) is unknown.

The samples are examined randomly and are all examined under the same conditions (either stable or biased), and therefore, the calculated medians of all four groups reflect the same performance. This means that the fractional bias is the same for all groups measured on the same instruments within a certain time interval, but distributed according to the individual SE_G.

$$\phi bias = M_C / T_M \text{ or percentage bias} = 100 * (\phi bias - 1)$$

Individual estimates of bias

The percentages of bias from the individual groups are totally independent estimates of the same bias, so the mean of these bias is assumed to be the best estimate of the actual bias.

Ranges of estimates

As each SE_G is unknown, but important for the estimates of bias, so the maximum range between two or more estimates of bias from the different groups defines the limits for the bias, i.e. this interval is the largest distribution of positive and negative values of bias. The mean bias could be used for corrections, but the maximum range (%) would define the uncertainty of the correction. This range, however, corresponds to more than two times the performance specifications (positive and negative), so the maximum half-range of bias values, can be compared directly to the classification specifications, when the correction is performed.

Results

Target values

In Table 1, the target values for the medians are based on the raw data for creatinine medians for serum and plasma from the nine last months of 2017 and these are supported by the means of the medians from 2014 to March 2017.

There was no detectable difference between the results from serum and plasma samples. By changing from serum to plasma creatinine, there was no systematic change and the Deming regression line was plasma = 0.9916 serum + 1.0193 within the range 25–1000 μmol/L.

Medians

The dispersion of monthly median concentrations is illustrated in Figure 1A and the closeness among the gender medians over time are illustrated in Figure 1B for the genders between 18 and 70 years and for the genders >70 years in Figure 1C. In both Figure 1B and C, the data are adapted to their target values, and the three levels of examination bias from the targets are illustrated with the horizontal lines. Likewise, the weekly medians are shown in Supplementary Figure 1A and B, and daily medians in Supplementary Figure 2A and B for the genders between 18 and 70 years and for the genders >70 years in A and B, respectively, and all adjusted to their target values. The calculated characteristics for daily, weekly and monthly medians of plasma creatinine from the four groups (combined from the three instruments) are presented in Supplementary Table 1.

Bias

The estimated daily, weekly and monthly bias for the four groups and their means are shown in Tables 2–4 with

Table 1: Target values based on serum and plasma creatinine medians in 2017 (from April).

Gender		Males		Females
Age, years	18–70	>70	18–70	>70
Target median, μmol/L[a]	79.0	88.5	62.6	69.1
Mean of medians, μmol/L 2014–March 2017[b]	79	89	63	69

[a]Medians calculated after April 2017 are with one significant figure after the decimal point on plasma and serum samples. [b]Medians calculated before April 2017 are integers.

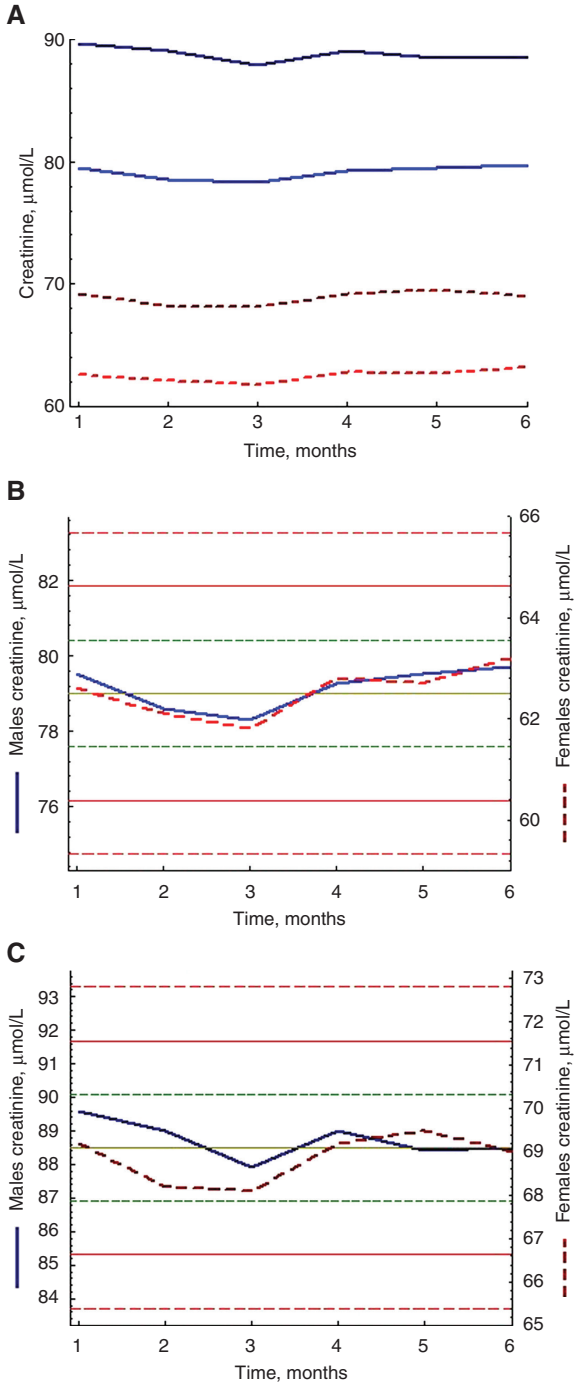

Figure 1: Monthly median creatinine plasma concentrations for the six first months of 2018.
(A) The four groups: males (M): (M 18–70) (solid light blue), (M >70) (solid dark blue), females (F): (F 18–70) (dotted light red) and (F >70) (dotted dark red). (B) The medians by gender in 18–70 years, where the ordinates are adjusted to the target values (M 18–70): 79.0 µmol/L and (F 18–70): 62.6 µmol/L (same colours as in Figure 1A). (C) The medians by gender >70 years, where the ordinates are adjusted to the target values (M >70): 88.5 µmol/L and (F >70): 69.1 µmol/L (same colours as in Figure 1A). The horizontal lines in the figures (B and C) are the targets (dark yellow), optimum for ϕbias, ±1.8% (green dotted), desirable, ±3.6% (red) and minimum quality, ±5.4% (red dotted).

maximum half-range and classifications of quality for each according to the APS described. The four groups of monthly bias are illustrated together with the mean bias in Figure 2. The corresponding weekly medians with bias are shown in Figure 3A, whereas the weekly results for the instrument Vista 3 are illustrated in Figure 3B. The three levels of examination bias from the targets are illustrated by the horizontal lines.

Discussion

Target values and analytical stability

Traceability of measurands is central in laboratory medicine, but may be costly to attain and may need considerable resources every time new calibration or reagents are introduced if traceability is to be maintained. If this process could be restricted to be performed, e.g. once every year or second year, it would save financial and other resources. However, the assessment of analytical stability in the time between the traceability processes, through use of frozen sera in daily internal control strategies, is also costly, and the materials used may not be sufficiently commutable. Samples from patients, however, are commutable, by definition, and are available and costless if adopted for quality management: thus, by use of calculated patient medians, the examination stability can be assessed [1, 2] for most measurands in laboratory medicine without biological rhythms. This method has been improved for serum sodium [3] by separating the medians by gender, in order to get two independent estimates of bias, which can confirm (or refute) each other. A similar approach was used for serum albumin, where the medians by gender were restricted to results requested by GP, which solved the problem of albumin dependence on posture, since all these patients underwent phlebotomy in a sitting position [4]. For the use of medians in validation of analytical stability, it is vital to calculate the measurand concentrations directly from the raw data in order to obtain the needed accuracy to estimate the analytical bias, e.g. creatinine mean of the monthly bias for females (18–70 years) is +0.11% (Table 4); without the needed decimals, the estimate would have been 0%, and the target and bias concentrations would both be 63 µmol/L.

For plasma creatinine, higher concentrations are found at the age of 70 years [7], and recently a publication (in Swedish) of even higher RIs for males (63–158 µmol/L) and females (51–136 µmol/L) of 80 years has been published [9], which confirms our further partitioning

Table 2: Performance bias for plasma creatinine (January–June 2018). Daily bias for plasma creatinine concentration medians by genders and age for all analysers.

Gender	Males	Males	Females	Females	All four groups	Two groups
Day/age, years	18–70	>70	18–70	>70	>18	18–70
Target, µmol/L	79.0	88.5	62.6	69.1		
Median, µmol/L	79.1	88.8	62.5	68.8		
Mean bias, %	0.21	0.41	−0.04	−0.32	0.07	0.09
Maximum half-range, %					5.18	1.89
Classification[a]					3	2

[a]Classification: "1" for half-range <1.8%, "2" for half-range <3.6%, "3" for half-range <5.4%, and "4" for larger half-ranges according to Fraser et al. [5].

Table 3: Performance bias for plasma creatinine (January–June 2018). Weekly bias for plasma creatinine concentration medians by gender and age for all analysers.

Gender	Males	Males	Females	Females	All four groups	Two groups
Week/age, years	18–70	>70	18–70	>70	>18	18–70
Target, µmol/L	79.0	88.5	62.6	69.1		
Median, µmol/L	79.1	88.8	62.6	68.9		
Mean bias, %	0.13	0.31	−0.09	−0.42	−0.02	0.02
Maximum half-range, %					2.44	0.91
Classification[a]					2	1

[a]Classification: "1" for half-range <1.8%, "2" for half-range <3.6%, "3" for half-range <5.4%, and "4" for larger half-ranges according to Fraser et al. [5].

Table 4: Performance bias for plasma creatinine (January–June 2018). Monthly bias for plasma creatinine concentration medians by gender and age for all analysers.

Gender	Males	Males	Females	Females	All four groups	Two groups
Month/age, years	18–70	>70	18–70	>70	>18	18–70
Target, µmol/L	79.0	88.5	62.6	69.1		
Median, µmol/L	79.4	88.8	62.7	69.1		
Mean bias, %	0.18	0.26	−0.11	−0.34	0.00	0.04
Maximum half-range, %					0.93	0.32
Classification[a]					1	1

[a]Classification: "1" for half-range <1.8%, "2" for half-range <3.6%, "3" for half-range <5.4%, and "4" for larger half-ranges according to Fraser et al. [5].

of the medians by gender into groups below and above 70 years. This provides four medians in the concentration interval 62–88 µmol/L, as shown in Table 1 and Figure 1A.

Variations in estimates of examination stability

All patient results are influenced by the same examination performance and, when this is proportional, all results from patient are affected by the same fractional error or percentage error. The assumed proportionality is confirmed by the maximum half-range results for bias which, for monthly results, reduces to 0.32% for the two groups (males and females 18–70 years), but to 0.93% for all four groups, as shown in Table 4, due to the less stable T_G for males >70 years.

Long-term stability and minor errors in the instrument Vista 3

The means of monthly medians for all four groups are within 0.5% of their targets, which indicates considerable

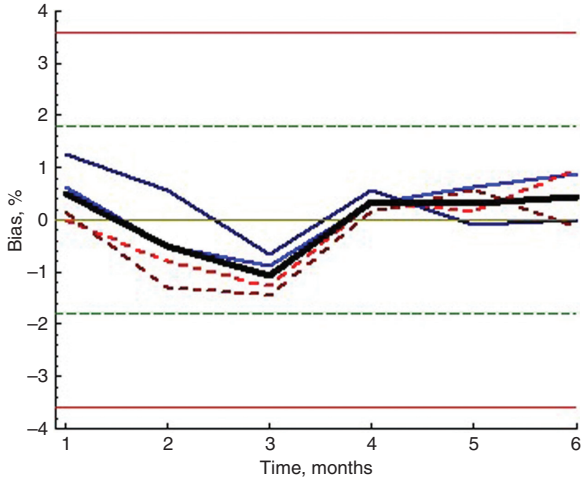

Figure 2: Monthly bias estimated from deviations of medians from their targets.
Bias for the four groups and for the mean of all four. (M 18–70) (solid light blue), (M >70) (solid dark blue), (F 18–70) (dotted light red), (F >70) (dotted dark red) and mean bias (thick black line). The horizontal lines are the targets (dark yellow), optimum for ϕbias, ±1.8% (green dotted), desirable, ±3.6% (red) and minimum quality, ±5.4% (red dotted).

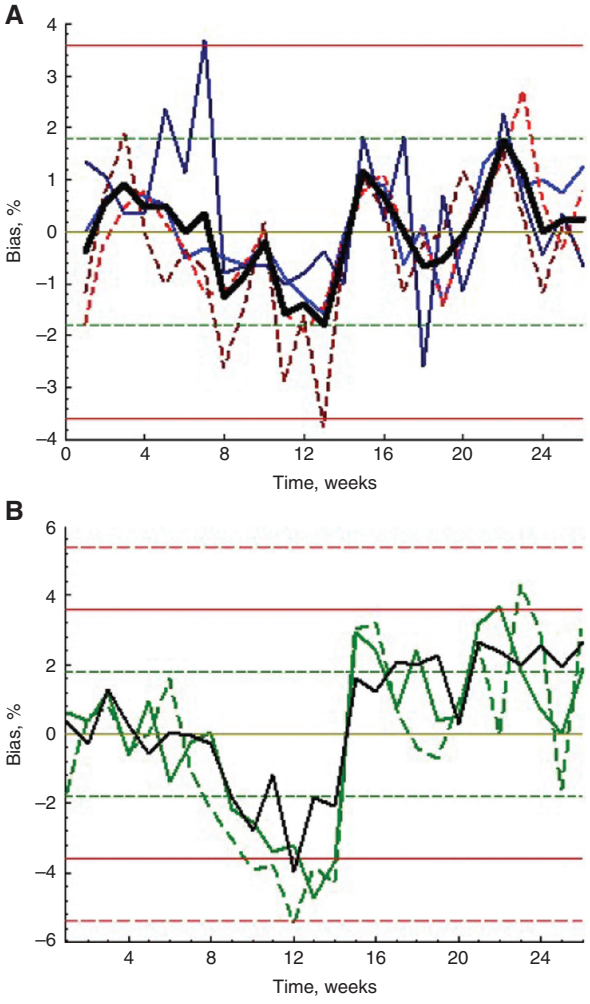

Figure 3: Weekly bias estimated from deviations of medians from their targets.
(A) Bias for the four groups and for the mean of all four. (M 18–70) (solid light blue), (M >70) (solid dark blue), (F 18–70) (dotted light red), (F >70) (dotted dark red) and mean bias (thick black line). (B) Weekly bias for the single instrument Vista3. The curves are (M 18–70): (solid green), (F 18–70): (dotted green) together with the frozen serum control (solid black). The horizontal lines are the zero bias (dark yellow), optimum for ϕbias, ±1.8% (green dotted), desirable, ±3.6% (red) and minimum quality, ±5.4% (red dotted).

long-term stability within the optimum APS during this study (Table 4), but the daily, weekly and monthly medians for individual instruments might disclose general or local errors in the three instruments. Thus, the Vista 3 showed a bias of approximately –4% after new calibration at week 9, and a new bias of approximately +2% at a renewed calibration in week 15 as described in Figure 3B. This minor deviation introduced in week 9 is also reflected in the combined weekly bias plot (Figure 3A), but only to the level of approximately –1.5% and not much in evidence from week 15. This situation can be compared to our results for serum albumin, where a comparable bias was found for all three instruments and could be assigned to the common calibrator and reagents [4]. The effect is also seen in the monthly bias plot (Figure 2). The bias was not disclosed by the routine procedure since this was within the acceptance limits (±4.4 µmol/L) laid down for accreditation in Hillerød.

Relationship between the bias the maximum half-range and analytical performance specifications

The use of bias is likely to be easy to understand, but the half-range and the relation between the maximum half-range and APS are more complicated.

In Figure 3A, the four estimates of bias at week 9 are (M 18–70): –0.63%, (M >70): –0.68%, (F 18–70): –0.64% and (F >70): –1.45%, and the mean bias is –0.85%. The correction of bias is then –0.85%. But the range of all four estimates is 0.81% (from –0.64% to –1.45%). After correction using –0.85%, the individual bias values change to +0.22%, +0.17%, +0.21% and –0.60%. Thus, the corrected result is an unbiased value with the four estimates scattered around zero defining the range of individual estimates of bias. This scatter is only of a small range (for week 9), but varies for the different weeks and the maximum half-range defines the largest deviation

from the mean correction. This deviation from the mean of the individual estimates is larger than the uncertainty of the mean estimate and defines a maximum error of the correction, and it is therefore comparable to the APS, which define the maximum allowable bias for use of common RIs [5].

The maximum weekly half-range for bias of the four groups is 2.44% (Table 3) which is comparable with the desirable APS for bias (3.6% [5]) and thus describe the weekly performance as clearly sufficient within the concentration range of 60–90 µmol/L.

Furthermore, corrections with the calculated monthly bias will maintain the corrected monthly bias within 0.93%, which is about half of the desirable APS of 1.8%.

Had we used only the two estimates of bias from males and females from 18 to 70 years in the correction, where the weekly maximum half-range is 0.91% and the monthly is 0.32% (Tables 3 and 4), the performance quality could be further improved. This demonstrates a considerably possibility for obtaining even higher accuracy if needed, but it might result in frequent corrections. Thus, we suggest that the user of this approach objectively selects the number of medians to apply in the relevant strategy.

Use of daily, weekly and monthly bias in routine practice

The monthly bias provide documentation of the examination stability (Figure 2) whereas the weekly bias are more operational in the process of revealing minor systematic errors in single instruments, as described for the Vista 3 above, while the results for the individual instruments can be useful in trouble-shooting, to validate the instrument calibration and separate instrument changes, in contrast to the common reagents and calibrator numbers used in all instruments.

If the daily bias estimate is outside the minimum APS, the deviation is considerable. If beyond desirable APS, it should be regarded as a warning, and the result should be compared to the previous bias results, to see if there is a trend, which is confirmed or refuted by the weekly bias. The sharpest bias is the combination of both genders 18–70 years, so they should be the first to detect systematic errors from the bias; but the other medians can confirm or refute the result and be used in the final decision the next day. Consequently, the daily medians can be used in the daily trouble-shooting for major problems, the weekly medians to disclose minor errors and the monthly medians to assess the long-term stability.

Plasma creatinine concentration and estimated glomerular filtration rate (eGFR)

Plasma creatinine concentration is the base in the calculation of eGFR, through use of a complicated formula, which is normalised to a standard body surface area of 1.73 m^2 (mL min^{-1} [1.73 m^2]$^{-1}$), but also related to age and gender, and sometimes race [10]. eGFR is of vital importance for the correct classification of chronic kidney disease, so the consequence of a biased plasma creatinine result may be erroneous diagnosis. A recent publication indicates that an analytical error to eGFR is acceptable if it does not exceed 10% [11], and thus recommend that the limit for analytical bias is 5% for plasma creatinine concentrations above 100 µmol/L. This recommended limit for bias is practically the same as the daily maximum half-range (%) for the four groups (Table 2), so our separation of medians by gender and age is also clinical useful, and will be valuable for most large clinical laboratories, using enzymatic methods to plasma creatinine measurements. The other creatinine methods based on Jaffè-endpoint, Jaffè-kinetic and Jaffè-compensated are non-specific, and cannot be compensated by intensive standardisation [11].

Ratios between patient medians partitioned by gender

For assessment of serum sodium [3] and serum albumin [4] using patient medians, we calculated ratios between the genders to validate the examination quality in relation to the APS. In the present study, we have used target values for plasma creatinine, which allows calculation of bias. The assessment of bias values is much easier to understand and apply, and we advocate use of these instead of ratios.

Conclusions

- Raw data from the analytical system are necessary to guarantee the number of significant figures in plasma creatinine results in order to generate patient medians with the needed accuracy.
- The daily medians are useful in the daily trouble-shooting of large systematic problems, the weekly medians in detecting minor biases and monthly medians in assessment of long-term analytical stability.
- Patient medians partitioned by gender and age are useful in assessment of examination stability within the plasma creatinine concentrations from 60 to 90 µmol/L.

- The mean of bias from medians by gender of patients 18–70 years of age are the most accurate for estimation of bias.
- The half-range of individual bias estimates are comparable to the APS and can classify the examination quality obtained as optimal, desirable or minimum quality.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organisation(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Lott JA, Smith DA, Mitchell LC, Moeschberger ML. Use of medians and "average of normals" of patients' data for assessment of long-term analytical stability. Clin Chem 1996;42:888–92.
2. Jørgensen LM, Hansen SI, Petersen PH, Sölétormos G. Median of patient results as a tool for assessment of analytical stability. Clin Chim Acta 2015;446:186–91.
3. Hansen SI, Petersen PH, Lund F, Fraser CG, Sölétormos G. Separate patient serum sodium medians from males and females provide independent information on analytical bias. Clin Chem Lab Med 2017;55:1865–72.
4. Hansen SI, Petersen PH, Lund F, Fraser CG, Sölétormos G. Gender-partitioned patient medians of serum albumin requested by general practitioners for the assessment of analytical stability. Clin Chem Lab Med 2017;56:843–50.
5. Fraser CG, Petersen PH, Libeer J-C, Ricós C. Proposals for setting generally applicable quality goals solely based on biology. Ann Clin Biochem 1997;34:8–12.
6. Rustad P, Felding P, Franzon L, Kairisto V, Lahti A, Mårtensson A, et al. The Nordic reference interval project 2000: recommended reference intervals for 25 common biochemical properties. Scand J Clin Lab Invest 2004;64:271–84.
7. Carlsson L, Lind L, Larsson A. Reference values for 27 clinical chemistry tests in 70-year-old males and females. Gerontology 2010;56:259–65.
8. Carobene A, Marino I, Coscum A, Serteser M, Unsal I, Guerra E, et al. The EuBIVAS project: within- and between-subject biological variation data for serum creatinine using enzymatic and alkaline picrate methods and implications for monitoring. Clin Chem 2017;63:1527–36.
9. Helmerson-Karlqvist J, Ridefelt P, Lind L, Larsson A. Normalvärden för 80-åriga män och kvinnor bosatta i Norden. Klinisk Biokemi i Norden 2018;30:26–30.
10. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5–18.
11. Jassam N, Weykamp C, Thomas A, Secchiero S, Sciacovelli L, Plebani M, et al. Post-standardization of routine creatinine assays: are they suitable for clinical applications. Ann Clin Biochem 2017;53:386–94.